NDA 020180/s034:
Proscar® (finasteride 5 mg tablet)

Indication: No new indication proposed

Applicant: Merck and Co., Inc.

FDA Presentation
ODAC Meeting
Dec. 1, 2010

NDA 020-180/034 Review Team

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Proscar: Key Proposed Labeling

- Clinical Studies Section
  - **Added** - "Other Studies"→ efficacy claim

- Adverse Reactions Section:
  - **Deleted** - "PROSCAR is not approved to reduce the risk of developing prostate cancer"
  - **Added** – detection bias may have led to the increased high-grade cancer on finasteride arm
  - **Added** - reference to ASCO/AUA guidelines

Key FDA Concerns: PCPT Results

1. Increased Risk for Gleason Score (GS) 7–10 Tumors.

2. Reduction in Risk Limited to GS $\leq$ 6 Tumors.

3. Results Generalizable to U.S. Population?

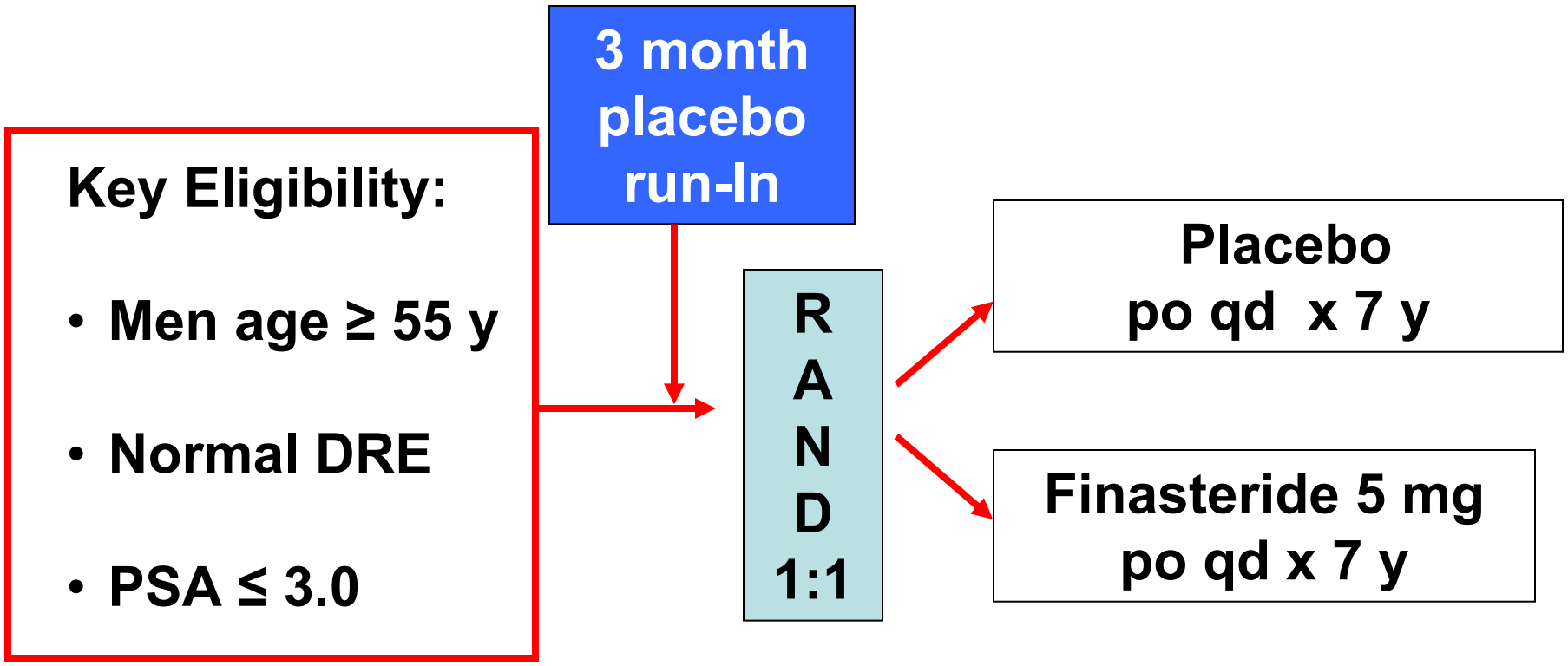
Outline of the Presentation

- FDA Concerns
- Key Regulatory History
- Prostate Cancer Prevention Trial Design
- FDA Review Of Efficacy
- FDA Review Of Safety

Regulatory History

June 1992	Original NDA approval
June 1993	IND submitted by SWOG for protocol SWOG-9217 (the Prostate Cancer Prevention Trial)
January 2002	Merck: data analysis plan
September 2003	Labeling revision: increased HG prostate cancer
January 2005	Proposed labeling revision: “de facto” efficacy claim
June 2005	Applicant withdrawal: proposed labeling revision including PCPT efficacy results
May-October 2009	At FDA request, Applicant resubmits PCPT efficacy and safety datasets

SWOG-9217 (PCPT) Study Design



Endpoints

Primary: Histologically proven presence/absence of prostate carcinoma after seven years

Secondary: Prostate cancer stage/grade

Statistical Plan

- Estimate: Prostate Cancer Prevalence 6% on Placebo
- 25% Reduction Considered Clinically Important
- 92% Power and 2-sided Type I Error of 5%
- Estimate: ~40% Drop-out / Refuse Prostate Biopsy
- Required Sample Size: 18,000 Men
- No Formal Early Stopping Rules or Interim Analysis

Study Assessments

- Annual DRE and PSA Test
  - Finasteride arm: adjusted PSA level
    e.g. 2.5 ng/mL x **2** (index factor) = 5
- Prostate Biopsy (6-core) Prompted by:
  - abnormal DRE
  - elevated PSA
  - high-grade PIN (re-biopsy)
  - scheduled 7 year end of study biopsy
- Centralized Path Review: Modified Gleason Score

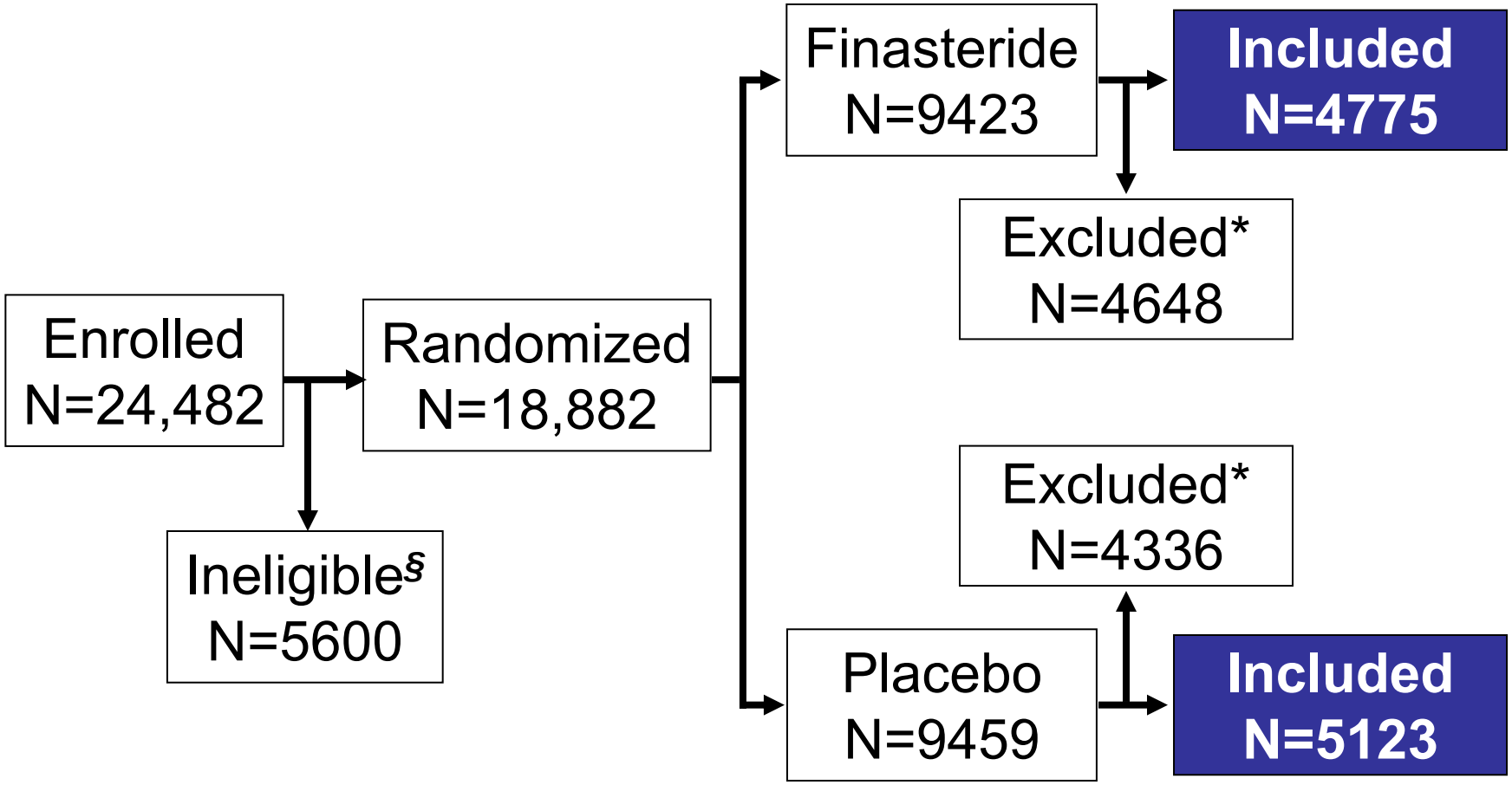
Key Study Revisions

- Increased PSA Index (2 to 2.3) Starting Year 4
- Revised Prostate Cancer Primary Endpoint
  - "Biopsy proven" to "histologically proven"
- Revised Prostate Biopsy Technique
  - Direct biopsy needle toward peripheral zone*
- Early Termination (DSMC Recommendation)

*Finasteride shrinks peri-urethral zone of prostate

PCPT Study Results

Disposition And Status



§PSA > 3 ng/mL in 70%

***Excluded if: (1) No prostate cancer diagnosis before year 7**
(2) No "End of Study" biopsy performed

Baseline Characteristics

(Primary Analysis Population)

- Median Age 62 (F) And 63 (P)
- Race
  - 92.7% (F) and 93.5% (P) Caucasian
  - 3.6% (F) and 3.2% (P) **African Americans**
- Prostate Cancer History 1° Relative: 17%
- Median PSA Value: 1.1 ng/mL
- Prior History Negative Prostate Biopsy: 7%

Risk Reduction of Prostate Cancer
(SWOG Population*)

	Finasteride N=4775	Placebo N=5123
Cumulative Incidence	**879 (18.4%)**	**1274 (24.9%)**
RR (95% CI) p value	0.74 (0.69, 0.80) <0.0001	
Relative Risk Reduction (95% CI)	26% (21.1%, 31.4%)	
Logistic Regression: **Odds Ratio (95% CI)** p-value	**0.68 (0.62, 0.75)** <0.0001	

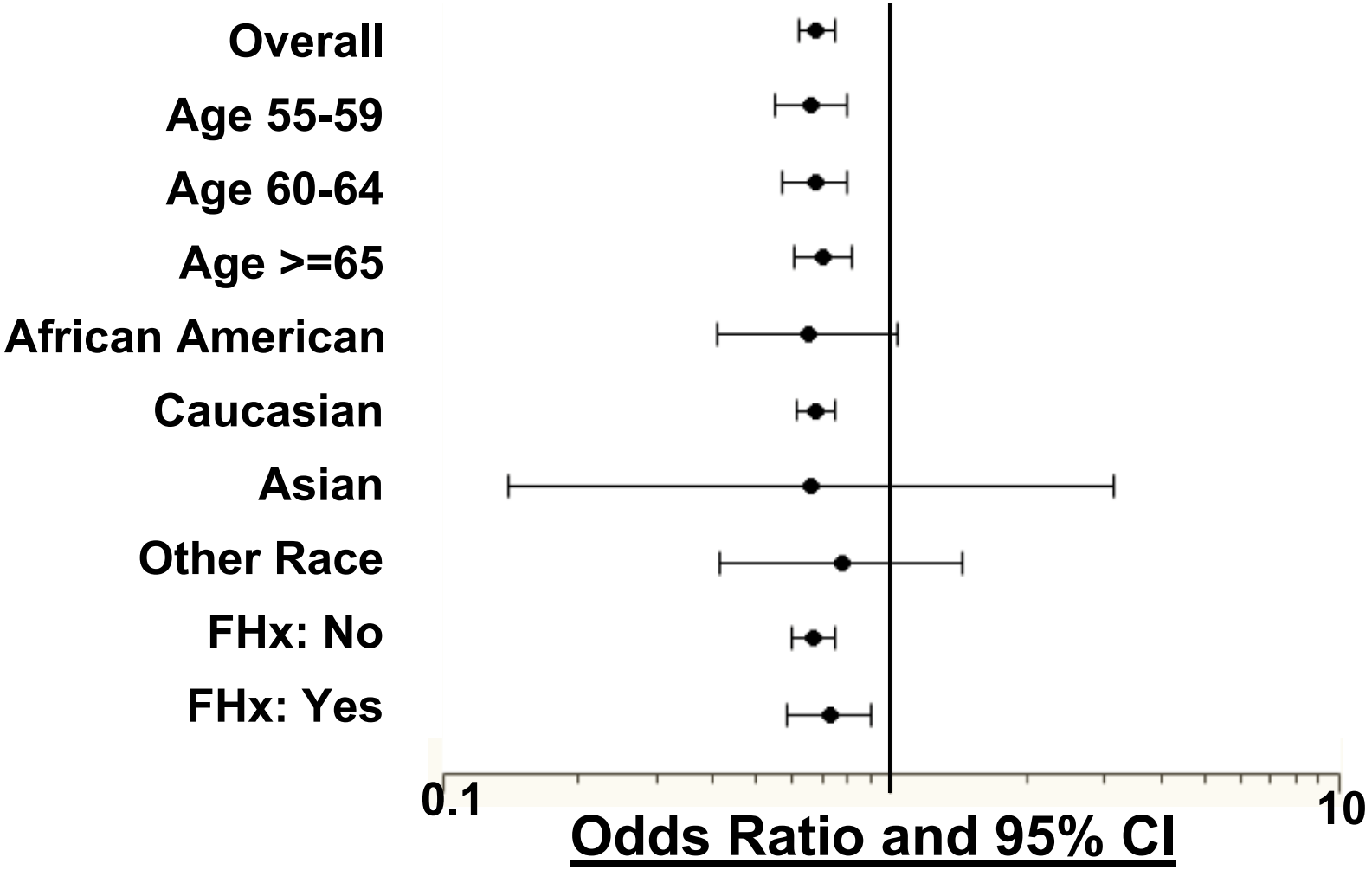
*Applicant's primary analysis population

Risk Reduction of Prostate Cancer
(Biopsied Population*)

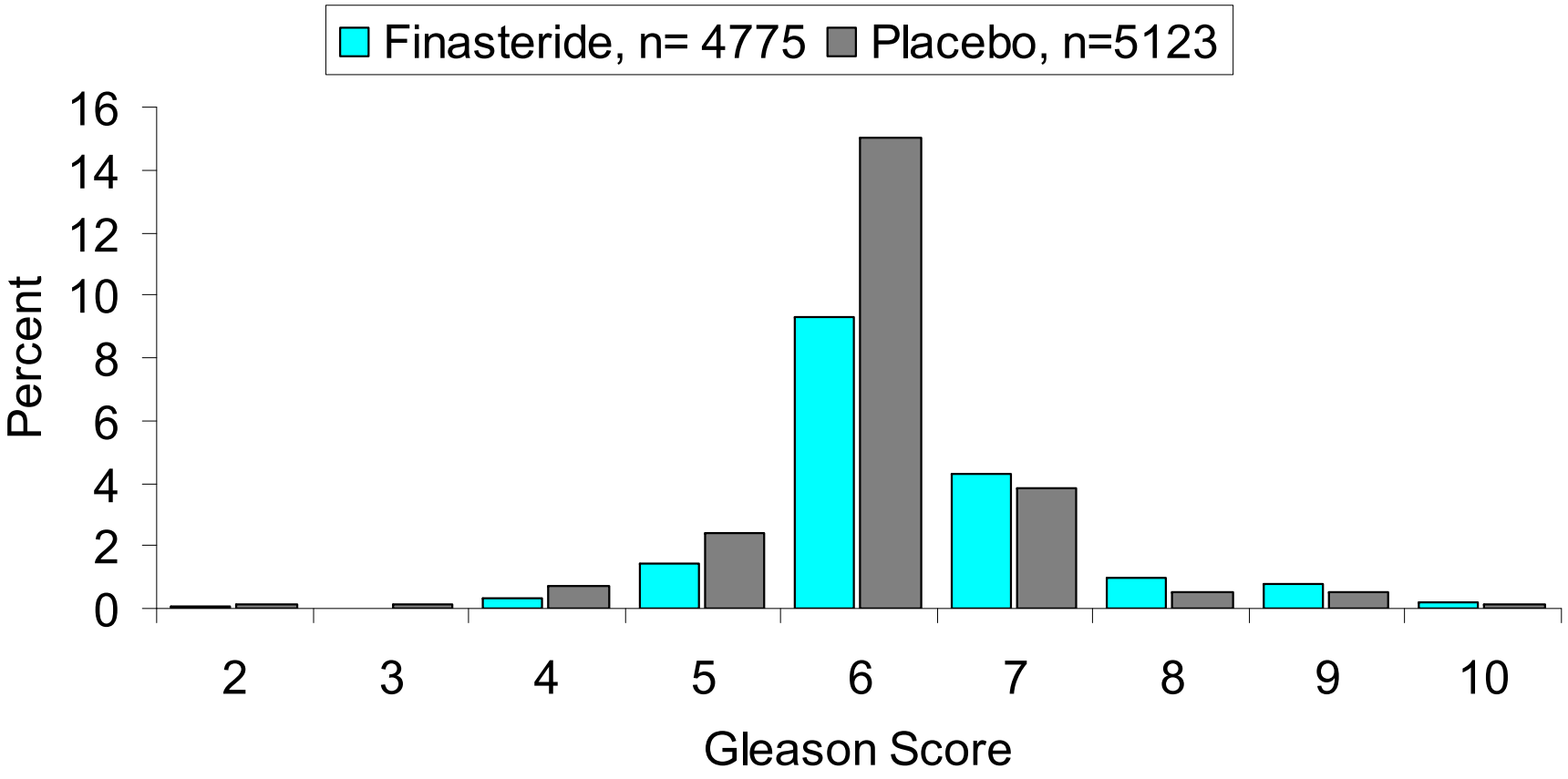
	Finasteride N=5297	Placebo N=5680
Cumulative Incidence	**879 (16.6%)**	**1274 (22.4%)**
RR (95% CI) p value	0.74 (0.69, 0.80) <0.0001	
Relative Risk Reduction (95% CI)	26% (21.1%, 31.5%)	

*Men who had at least one prostate specimen for diagnosis
FDA sensitivity analysis

Risk Reduction: Subgroups



Cumulative Incidence by Modified Gleason Score, SWOG Population

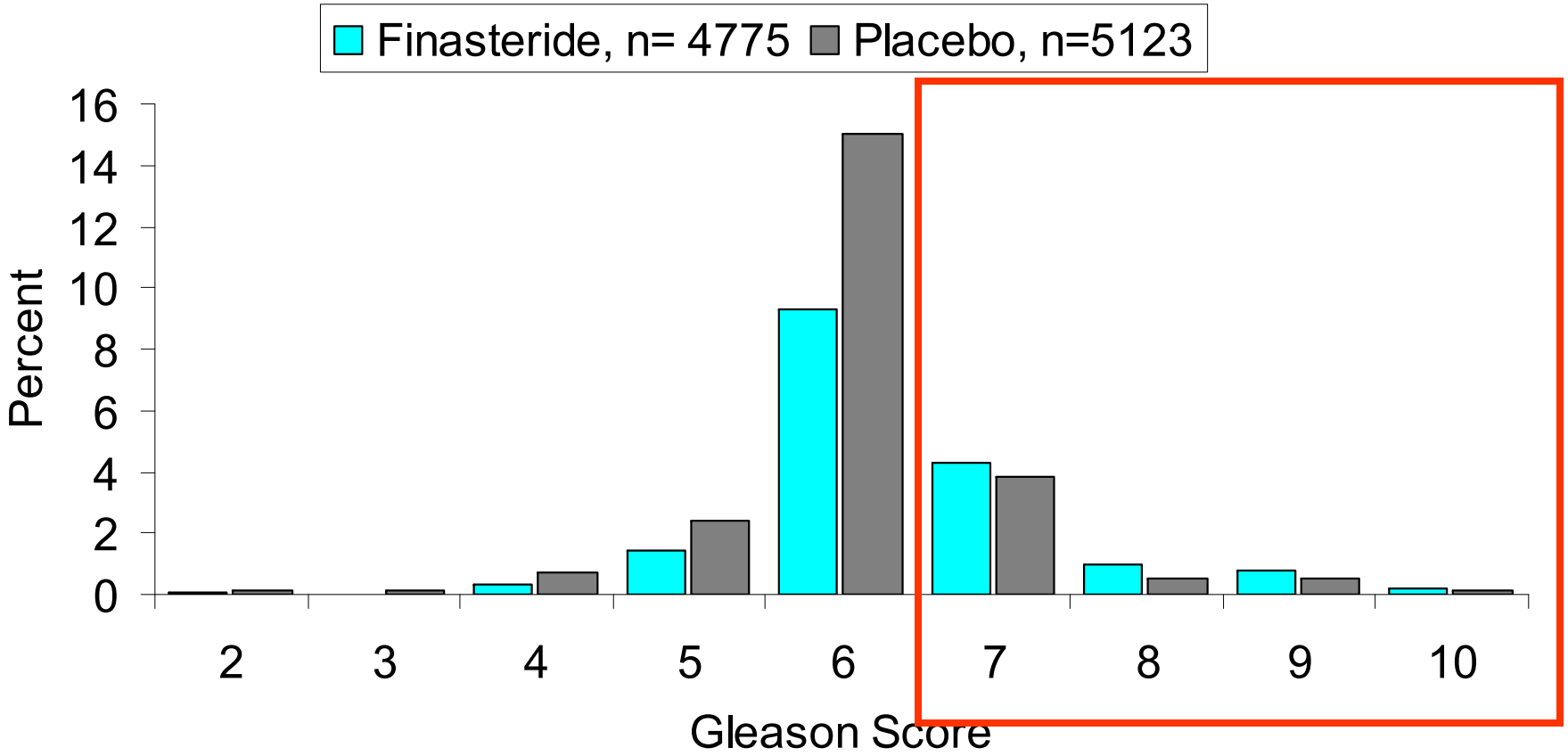


~ 95% of diagnosed cancers assigned a Gleason score

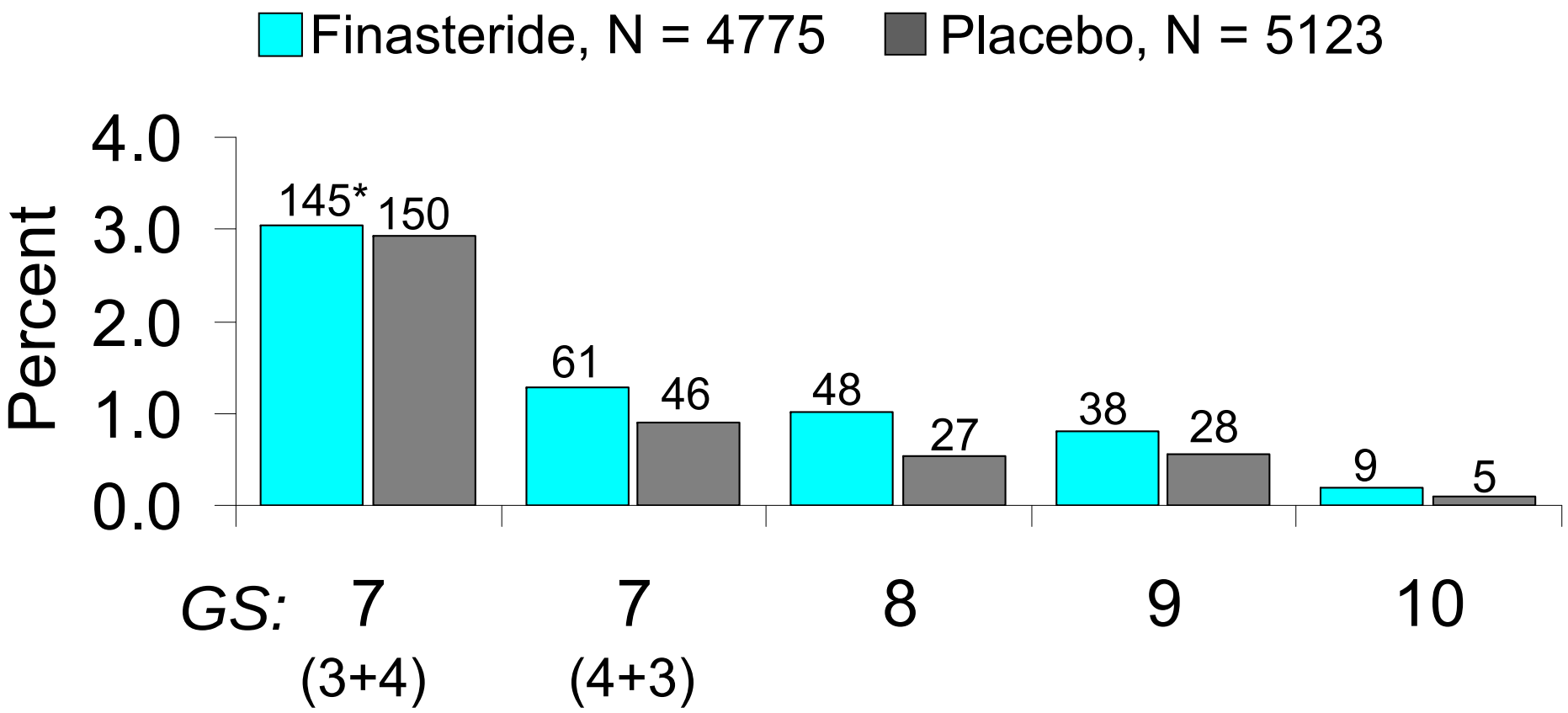
Key FDA Concerns: PCPT Results

1. Increased Risk for Gleason Score (GS) 7–10 Tumors.
2. Reduction In Risk Limited to GS $\leq$ 6 Tumors.
3. Results Generalizable to U.S. Population?

Issue 1: Increased High Grade Cancer



Issue 1: Increased High Grade Cancer



***Number of Cases**

Modified Gleason Score Category
(SWOG Population)

	Finasteride N=4775	Placebo N=5123	RR (95% CI)
Overall	879 (18.4%)	1274 (24.9%)	0.74 (0.69, 0.80)
GS 2-6	532 (11.1%)	945 (18.4%)	0.60 (0.55, 0.67)
GS 7-10	**301 (6.3%)**	**256 (5.0%)**	**1.26 (1.07, 1.48)**
GS 8-10	**95 (2.0%)**	**60 (1.2%)**	**1.70 (1.23, 2.34)**

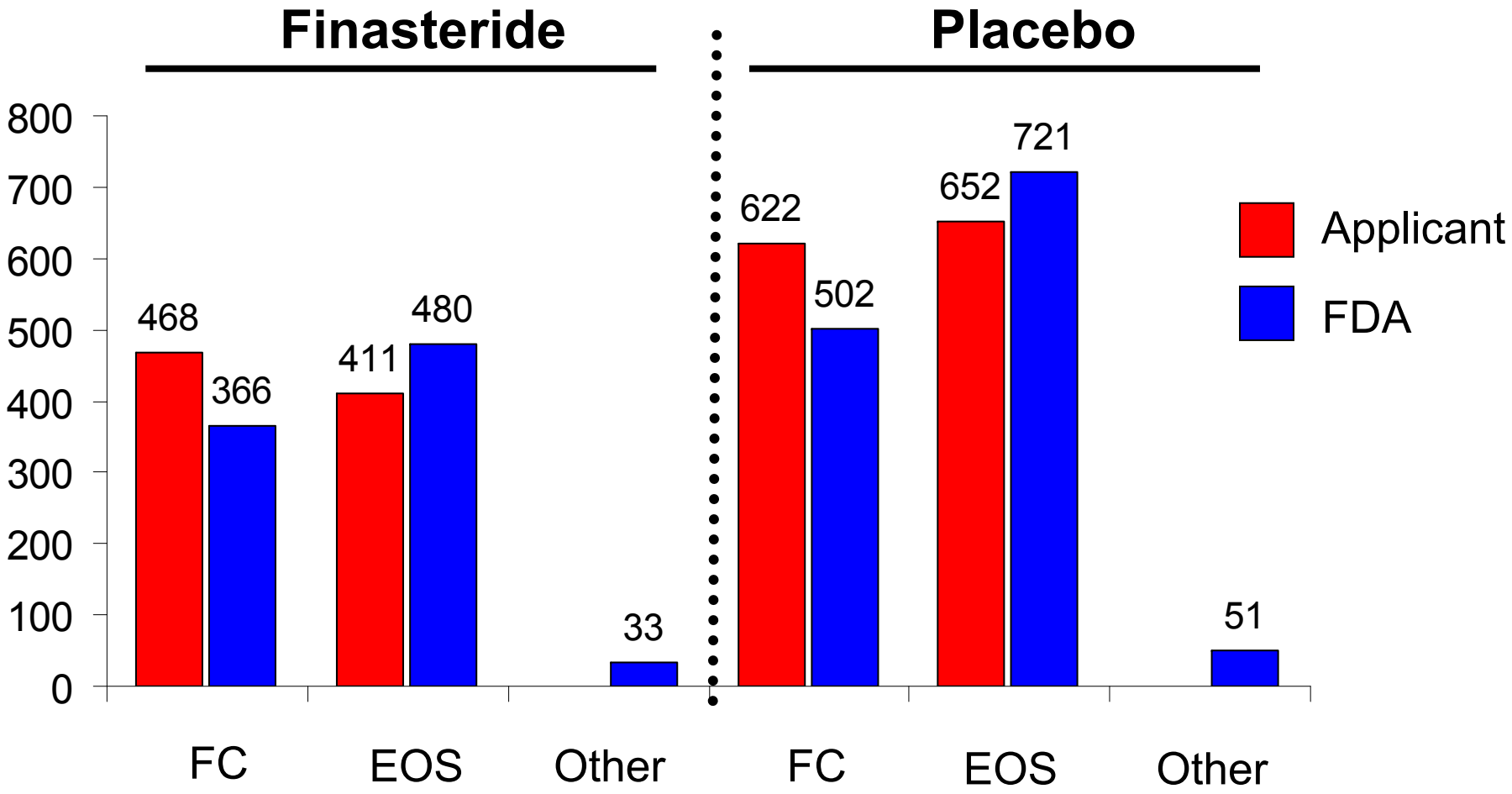
FDA Review: For Cause Cancers

- Applicant Definition of For Cause (FC):
  - Biopsies during the End of Study (EOS) biopsy window (7 yr ± 90 d) with elevated PSA /abnormal DRE
  - **All biopsies performed PRIOR TO the EOS biopsy window**

- FDA FC Definition: Biopsy Prompted by PSA Test/DRE

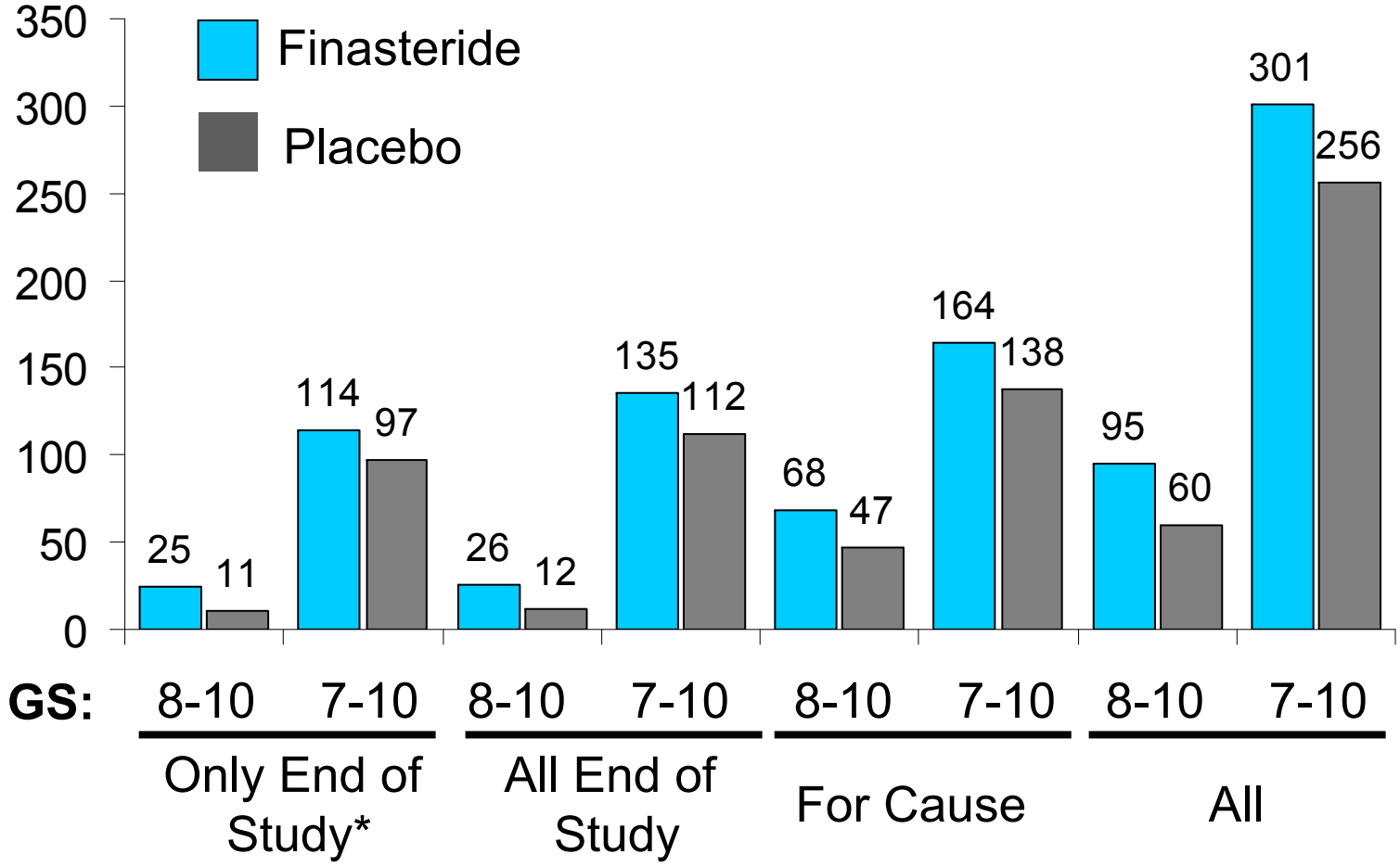
- FDA Review of Applicant FC Cancers
  - **149 FC cancers** were **EOS** scheduled biopsies
    - → FDA reclassified to **EOS**
  - **79 FC cancers** were **NOT** prompted by PSA / DRE
    - → FDA reclassified to **"Other"**

FDA Reclassification of EOS and FC Prostate Cancer



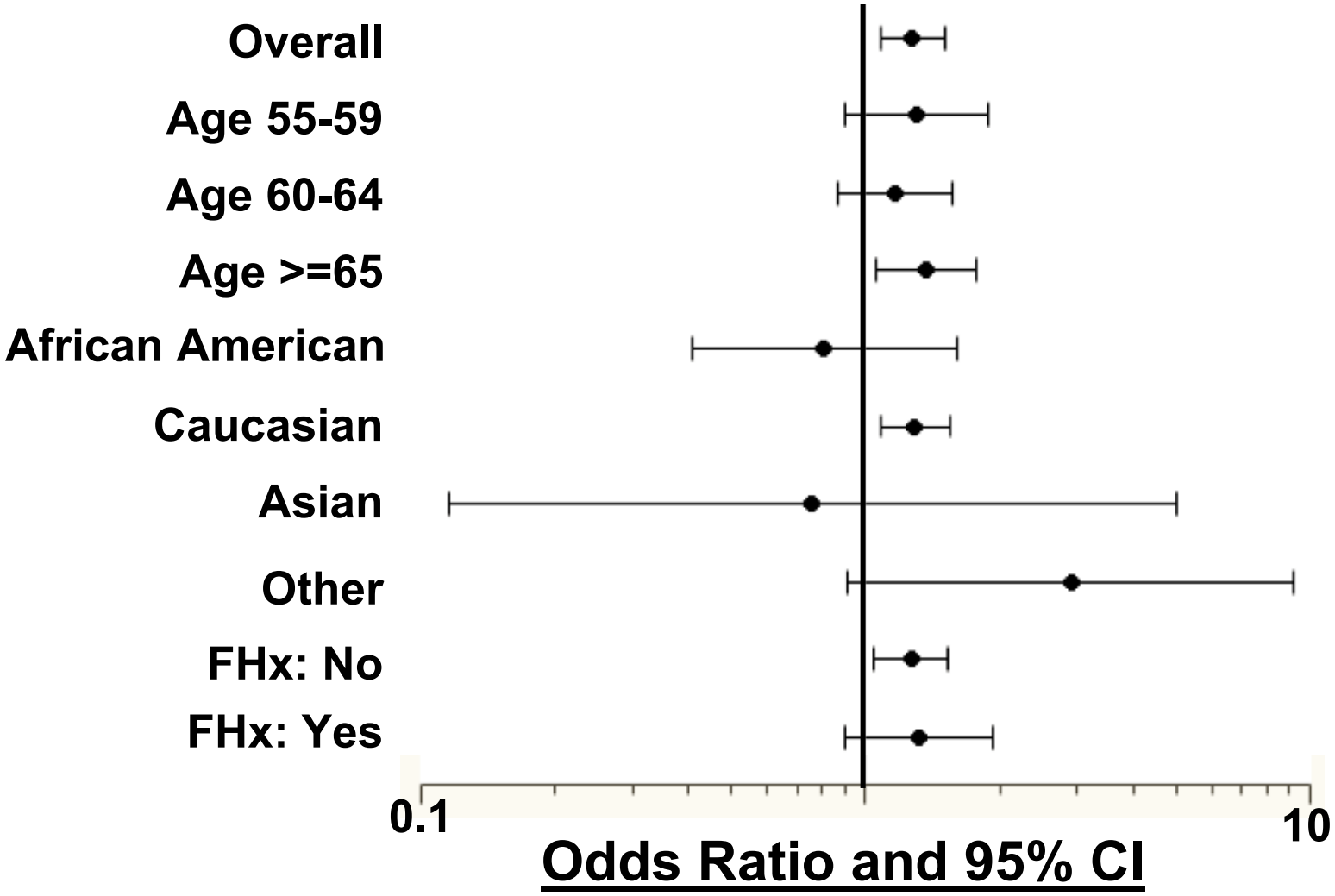
High-Grade Prostate Cancer, FC and EOS

FDA Classification



***First prostate specimen performed during scheduled EOS biopsy**

Increased GS 7-10 Cancer: Subgroups



Analyses Submitted in the Application to Explore the Increased High-Grade Cancer on Finasteride

Increased High-Grade Cancers: Post-hoc Analyses

- Exploratory Analyses→ Hypothesis Generation
- Uncontrolled Type I Error
- Over-reporting of Positive Results
- “Random High” Bias

Increased PSA/DRE Sensitivity

- **Sensitivity**: Probability of Positive PSA/DRE Test Given Positive Biopsy for Prostate Cancer

- **Hypothesis**: Increased PSA/DRE Sensitivity Led to Increased Incidence of HG Cancers on Finasteride

- **Issues:**
  1. HG cancers undiagnosed on placebo based on lower PSA/DRE sensitivity should be detected at EOS
  2. Increased HG on EOS biopsies

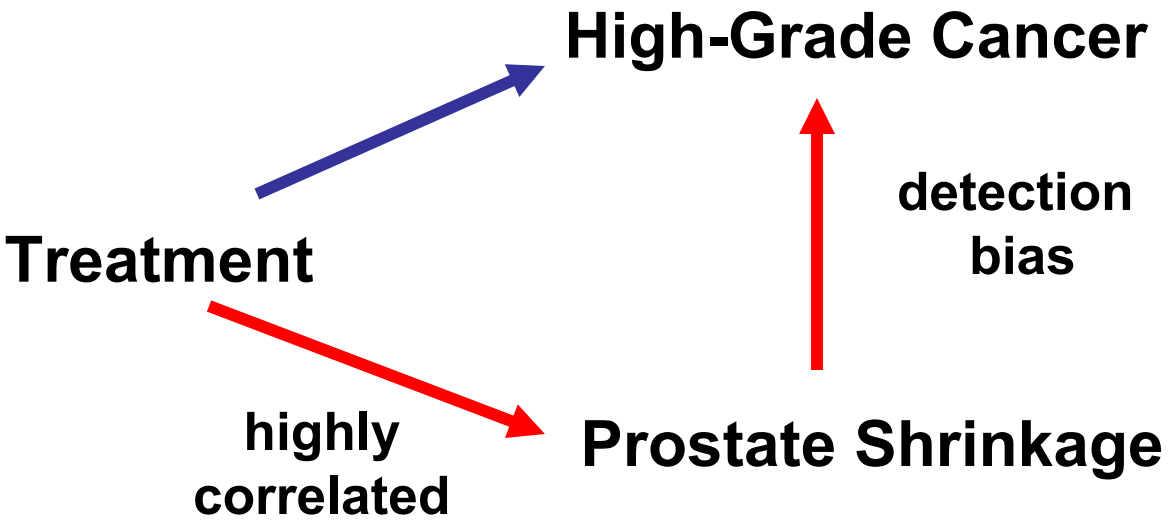
     GS 7-10: RR = 1.21 (95% CI 0.92, 1.58)

     GS 8-10: RR = 2.33 (95% CI 1.15, 4.74)

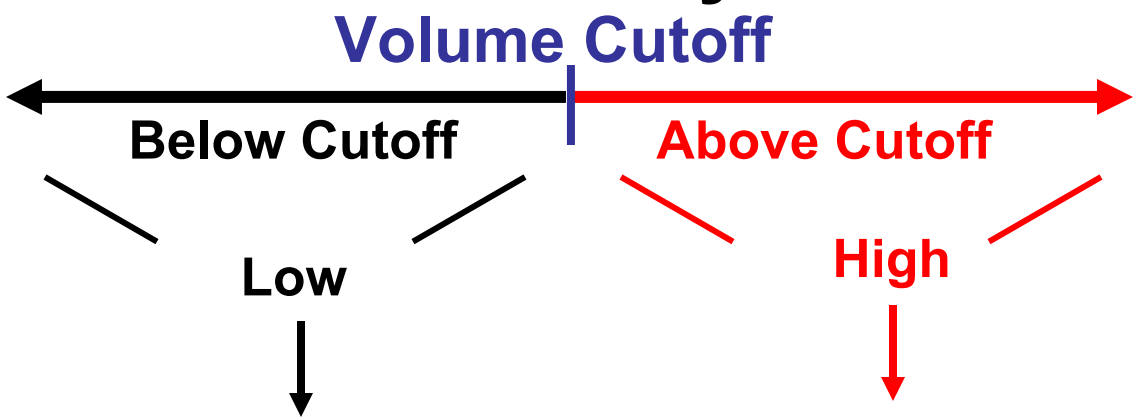
Detection Bias: Prostate Volume

- **Hypothesis**: Detection Bias Due to Prostate Shrinkage Resulted in Increased Incidence of HG Cancer on Finasteride

- Two Potential Causal Pathways:



Rate of HG Cancer by Treatment

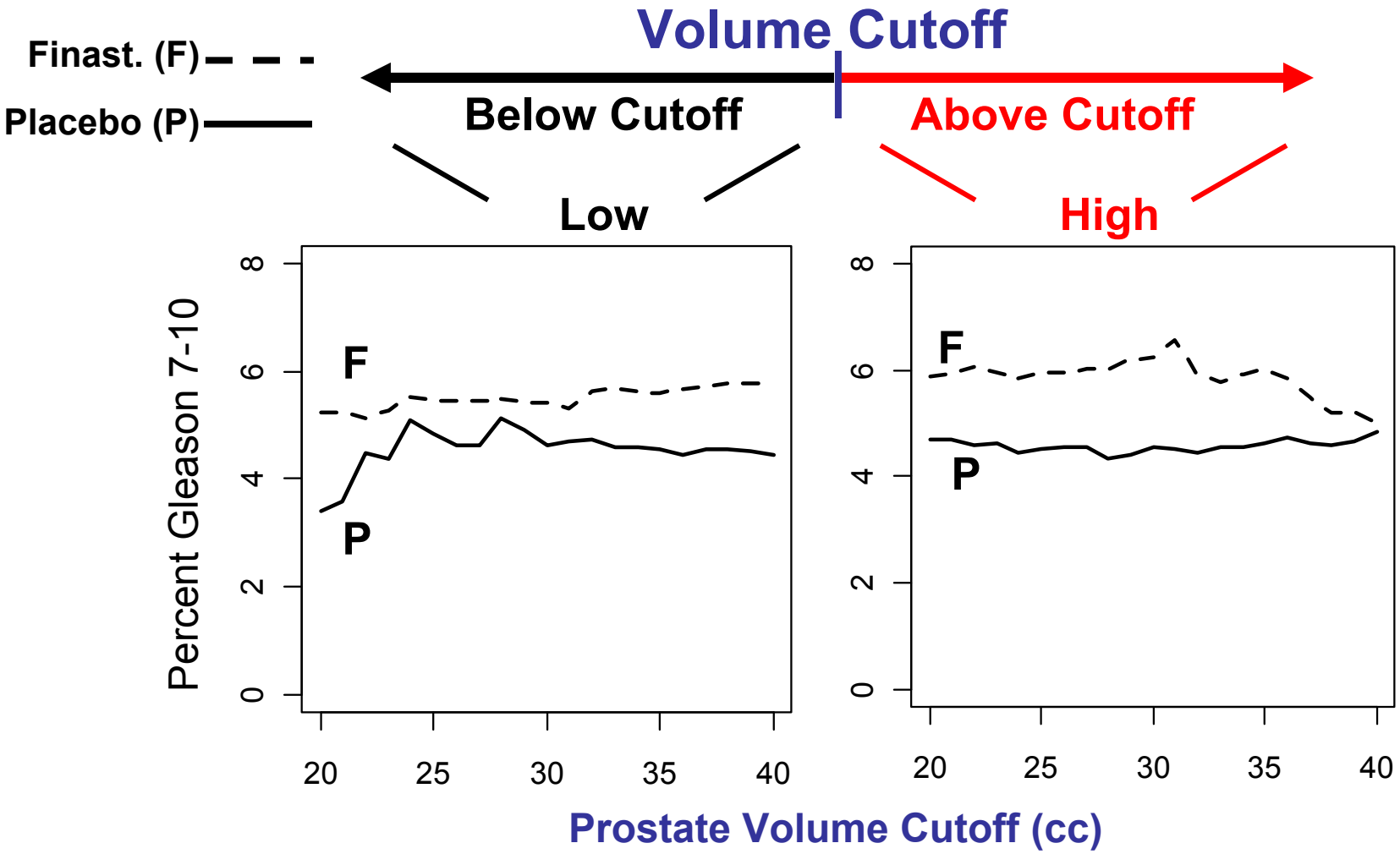


<u>Hypothesis</u>: detection bias due to decreased prostate volume

Rate should be higher on finasteride

Rate should be lower or the same on finasteride

Rate of HG Cancer by Treatment



- HG cancer rate: finasteride > placebo, both low and high volume groups

Prostatectomy Analyses

- Prostatectomy Sample Subgroup Represents ~25% of All Subjects Diagnosed with Cancer

- **Hypothesis**: HG Prostate Cancer NOT Increased in Prostatectomy Specimens

- **Issues**:
  1. NOT a random subgroup
  2. HG cancer risk on finasteride increased in this subset
     - GS 7-10: RR 1.19 (95% CI: 0.97, 1.46)
     - GS 8-10: RR 1.78 (95% CI: 0.96, 3.30)

Other Analyses: RRs (95% CI) for HG Cancer

	GS 7-10
Redman et al. (2008)	0.73 (0.56, 0.96)
Baker et al. (2010)	0.82 (0.64, 1.06)
Pinsky et al. (2008)	0.84 (0.68, 1.05)

Issue:

- Imputes >80% of cases (e.g. 929 cases imputed from 207 observed)

Other Analyses: RRs (95% CI) for HG Cancer

	GS 7-10	GS 8-10
Redman et al. (2008)	0.73 (0.56, 0.96)	1.25*
Baker et al. (2010)	0.82 (0.64, 1.06)	1.40 (0.71, 2.76)
Pinsky et al. (2008)	0.84 (0.68, 1.05)	1.39 (0.79, 2.50)

*No CI reported, said to be imprecise

Issue:

- Inconsistency between GS 7-10 and 8-10

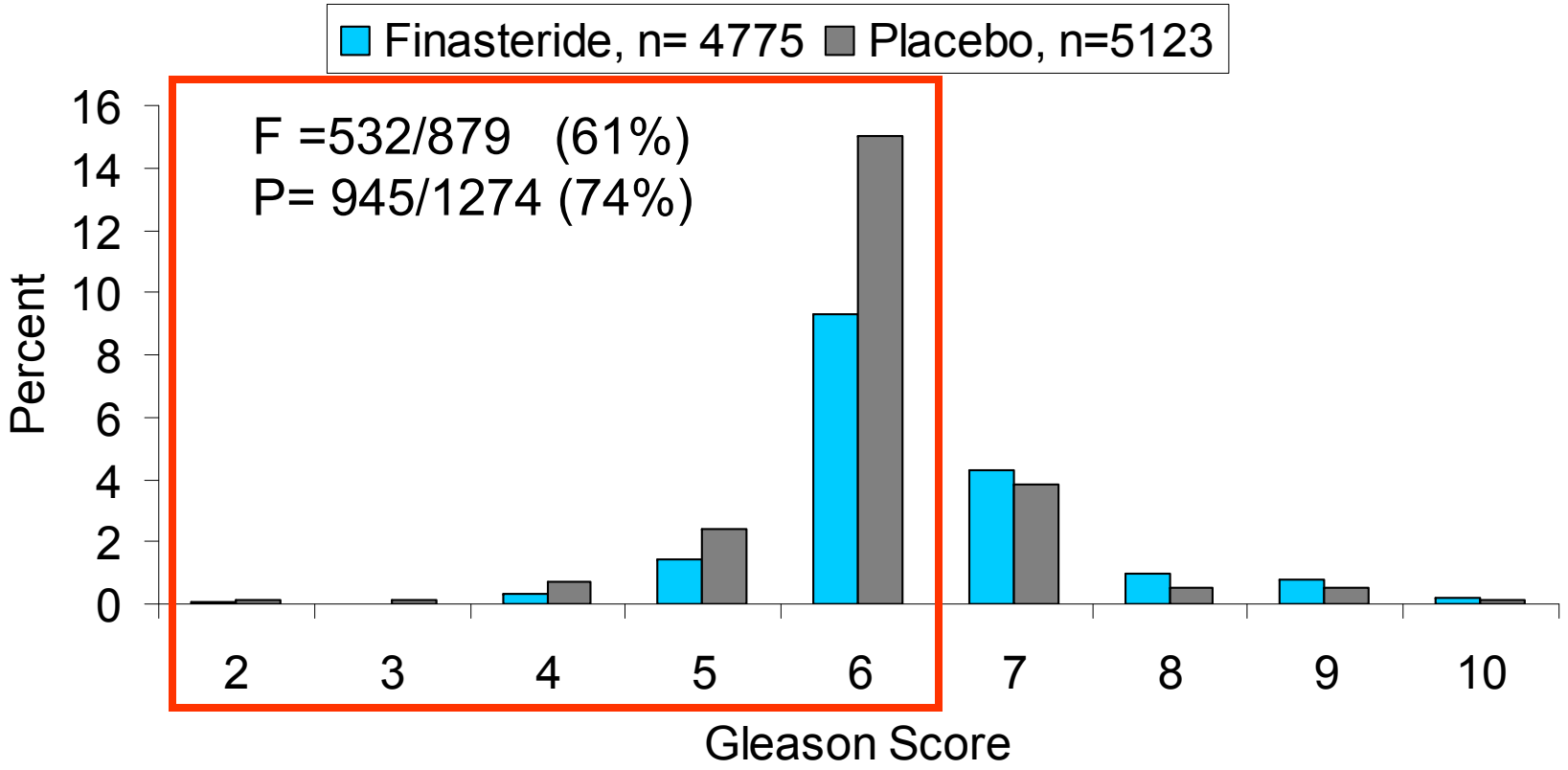
Summary: Post-hoc Analyses of HG Tumors

- Higher Sensitivity of PSA/DRE on Finasteride
  - ➢End of Study biopsy not dependent on PSA/DRE
- Detection Bias Due to Finasteride-Induced Prostate Shrinkage Led to Increased HG Cancers
  - ➢Prostate volume is post-randomization covariate highly correlated with treatment
- Use of Prostatectomy Data
  - ➢Missing data: imputes >80% of cases
  - ➢Opposing finasteride effect: GS 7-10 vs. GS 8-10
- Overall, GS 8-10 results are inconsistent with GS 7-10

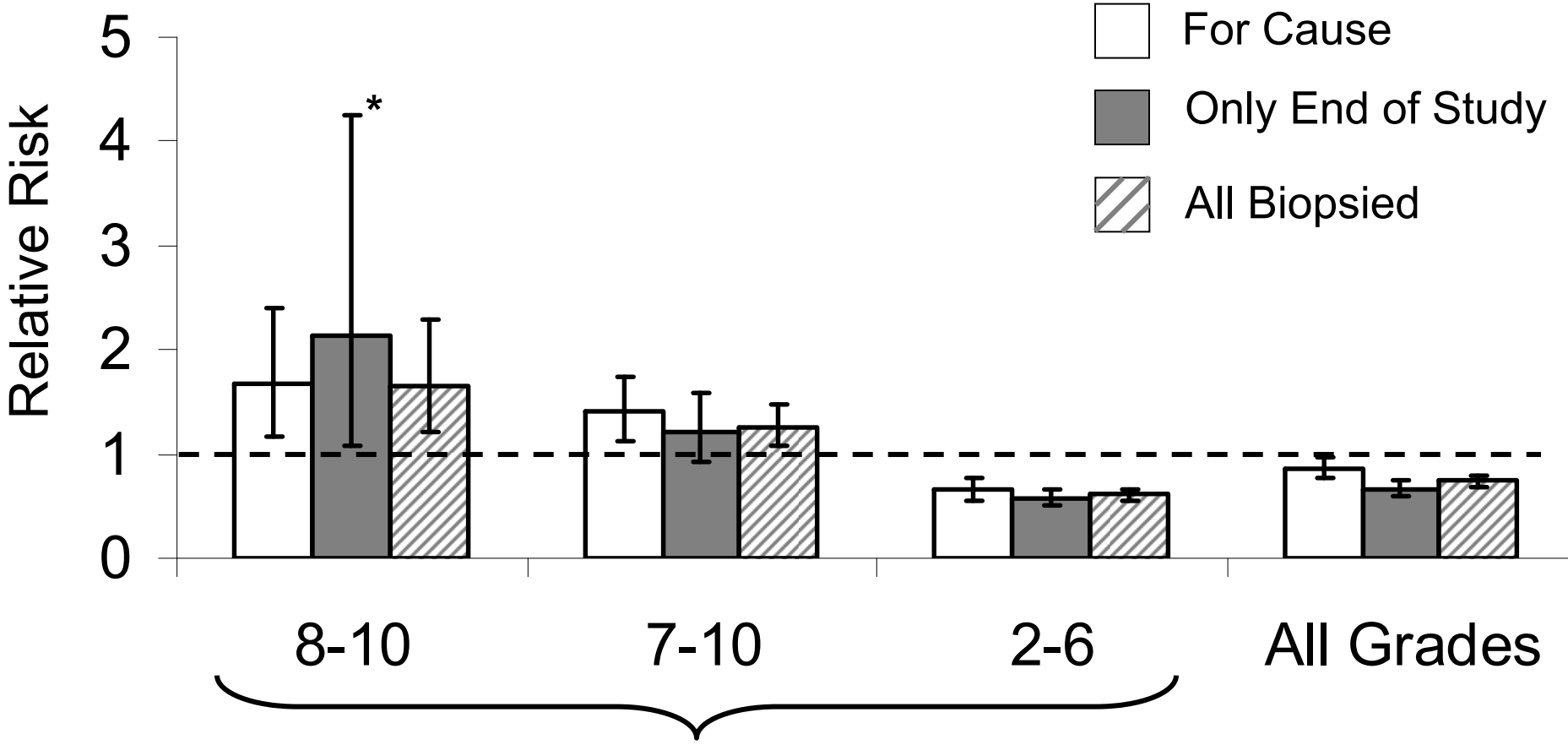
Key FDA Concerns: PCPT Results

1. Increased Risk for Gleason Score (GS) 7–10 Tumors.
2. Reduction in Risk Limited to GS $\leq$ 6 Tumors.
3. Results Generalizable to U.S. Population?

Issue 2: Risk Reduction Limited to Gleason Score ≤ 6 Tumors



Issue 2: Risk Reduction Limited to Gleason Score ≤ 6 Tumors



*Vertical lines: 95% CI

Issue 2: Risk Reduction Limited to Gleason Score ≤ 6 Tumors

- Lead Time Bias in Screen Detected Prostate Cancer
- GS ≤ 6 May Represent Latent Prostate Cancer
  - Concern for Over-Diagnosis
- Risk Stratification Employed for Management
  - **Low Risk:** GS ≤ 6 (no 4, 5); PSA < 10; T1-T2a tumors
  - **Very Low Risk:** GS ≤ 6 (no 4, 5); T1c; PSA density < 0.15 ng/mL/cm^3; ≤ 2 positive cores and ≤ 50% any core involved

Key FDA Concerns: PCPT Results

1. Increased Risk for Gleason Score (GS) 7–10 Tumors.
2. Reduction In Risk Limited to GS $\leq$ 6 Tumors.
3. Results Generalizable to U.S. Population?

Issue 3: Generalizability of Results

- Scheduled, Screening (End Of Study) Prostate Biopsies Not Consistent with Clinical Practice

- African American (AA) Men Under-represented
  - ~ 4% of men on PCPT were African American
  - Increased incidence rates compared to White men (232 per 100,000 vs. 146)
  - Increased death rates compared to White men (56 per 100,000 vs. 24)

Issue 3: Generalizability of Results

Scheduled End of Study Biopsy Only*

	Finasteride N=3906	Placebo N=4011	RR (95% CI)
Overall	422 (11%)	646 (16%)	0.67 (0.60, 0.75)
GS 2-6	304(7.8%)	541 (13%)	0.58 (0.50, 0.66)
GS 7-10	**114 (2.9%)**	**97 (2.4%)**	**1.21 (0.92, 1.58)**
GS 8-10	**25 (0.6%)**	**11 (0.3%)**	**2.33 (1.15, 4.74)**

*Exploratory analysis based on men undergoing only the end of study biopsy at 7 years

Benefit:Risk

The Number of Men Needed to Treat for:

- Reduction of One Prostate Cancer

  17 – 24*

- Reduction of One **For Cause** Prostate Cancer

  39 – 73*

- Development of One GS 7-10 Prostate Cancer

  115 – 205*

- Development of One GS 8-10 Prostate Cancer

  150 – 268*

*NNT range shown for “All Biopsied” and “ITT” populations

Key Safety Results

- Increased High-Grade Prostate Cancer on Finasteride

- On-study: 11 Patients Deaths due to Prostate Cancer
  - Finasteride, n=5
  - Placebo, n=6

- Most Common Adverse Events
  - Erectile dysfunction
  - Loss of libido
  - Gynecomastia

Summary: Risk/Benefit Analysis

1. Risk Increase for Gleason Score (GS) 7–10 Tumors
   - Consistent observation: For Cause, End of Study biopsies
   - Exploratory analyses of high-grade tumors not confirmatory

2. Risk Reduction Limited to Gleason Score $\leq$ 6 Tumors
   - Limited information on additional endpoints of clinical benefit to guide the regulatory decision

3. Generalizability of the Results
   - Scheduled, End of Study (screening) prostate biopsies to detect prostate cancer is not consistent with clinical practice
   - African Americans under-represented

4. Cancer Chemoprevention Indication

NDA 21319/s024:
AVODART® (dutasteride)

For "reduction in the risk of prostate cancer in men at increased risk"

Applicant: GlaxoSmithKline

FDA Presentation
ODAC Meeting
Dec.1, 2010

Proposed Indication

Newly Proposed (Oct. 25, 2010):

For reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA).

(Important Limitation Specified: AVODART is not indicated for the treatment of prostate cancer)

Key FDA Concerns

Issue 1: Risk of Avodart

- The increased risk for GS 8-10 prostate cancer
  - Observed consistently with either Original or Current Gleason scoring in both for-cause and scheduled biopsies
  - More evident with the Current Gleason scoring

    Estimated Treatment to Increased Risk Ratio for GS 8-10 Tumor: 200 to 1

- Is this increased risk for high grade prostate cancer clinically acceptable for prevention?

Key FDA Concerns

(Pertaining to the Proposed Indication)

Issue 2: Benefit of Avodart

- The risk reduction almost entirely limited to T1 ≤GS 6 tumors
  - Majority of the ≤GS 6 tumors represent very low risk prostate cancer by Epstein Criteria or NCCN Guidelines
  - Minority (20%) of the ≤GS 6 tumors may be clinically important
  - **Estimated Treatment/Prevention Ratio for possibly clinically meaningful prostate cancer*: 60 to 1**
- Is this risk reduction clinically meaningful for prevention?

*Including the small reduction in GS 7 tumor

Key FDA Concerns

Issue 3: Generalizability to Clinical Practice

- Time-mandated, repeated biopsies **without a clinical indication** NOT consistent with routine clinical practice
  - High prevalence of latent prostate cancer (40-70%)
- Only 2% of the enrolled men were Black
  - African American men at the high risk of developing prostate cancer

Presentation Outline

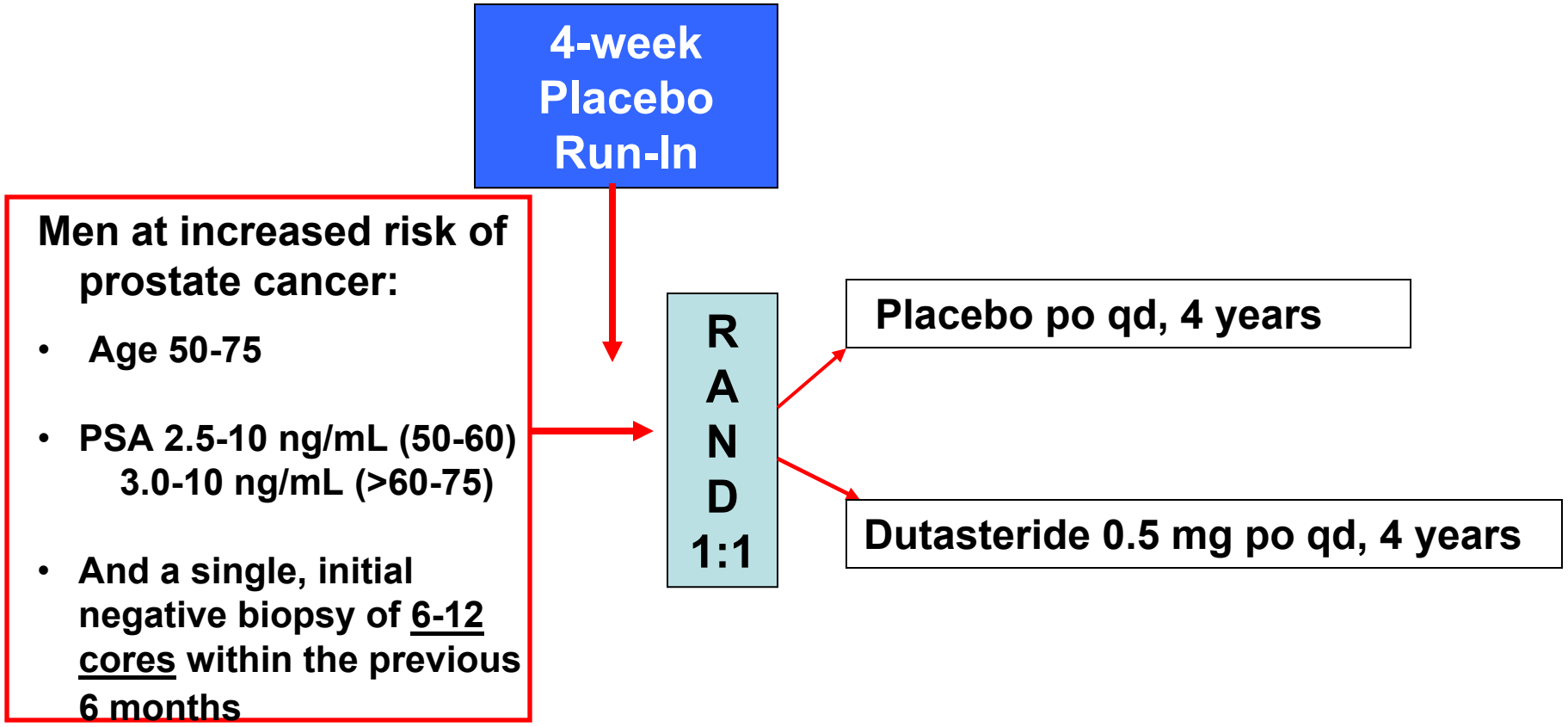
- Key FDA Concerns
- Regulatory History
- Study Design and Key Efficacy Results
- Clinical Relevance of the Efficacy Results
- Key Safety Results
- Summary and Benefit/Risk Analysis

Regulatory History

Nov 2001	Avodart (dutasteride, NDA 21-319) approved for the treatment of symptomatic BPH
Nov 2002	Study Protocol ARI40006 proposed for reduction of the risk of biopsy-detectable prostate cancer
Mar 2003- **May, 2009**	Protocol initiated Trial completed
Mar 2010	The sNDA re-submitted

The sNDA submitted initially in Sep. 2009, but withdrawn shortly for the investigator-study subject mismatches.

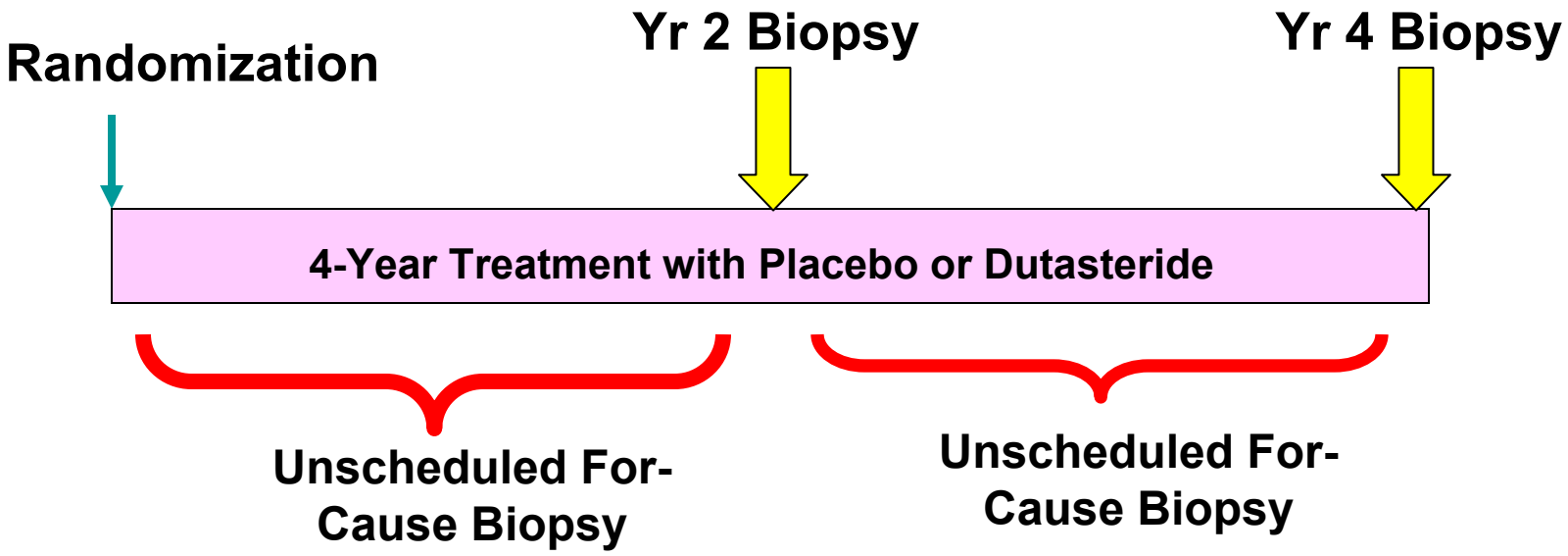
ARI40006 (REDUCE) Study Design



Endpoints

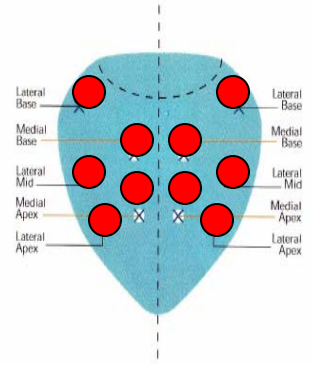
- **Primary:** Biopsy-detectable prostate cancer after 2 and 4 years
- **Key Secondary:** Gleason score of tumors at diagnosis

Efficacy Assessment: Biopsy-Detectable Prostate Cancer



Key Efficacy Related Elements:

- **Pre-defined TRUS 10 core biopsies: for Yrs 2 and 4 biopsies**
- **All biopsies: evaluated centrally using the Original Gleason Scoring system**
- **Treatment discontinued: if prostate cancer was diagnosed.**



Study Accrual

(20% of the patients from the US)

Geographic Region	Placebo (N=4126)	Dutasteride (N=4105)	Total N=8231 (%)
North America	1085	1100	2185 (26.5%)
USA	821	839	1660 (20.2%)
Canada	239	237	476 (5.8%)
Mexico	26	24	50 (0.6%)
Europe	2501	2471	4972 (60.4%)
South America	378	376	754 (9.2%)
Other*	162	158	320 (3.9%)

*Australia, New Zealand, Japan, South Africa

Baseline Characteristics

- **Demographics:** balanced between the arms:
  - Median age: 63 (59%<65; 41% ≥65)
  - Race: Caucasian 91%; **Black: 2%;** Other 7%
  - Family history of prostate cancer: 13%
- **Prostate Characteristics:** balanced between the arms
  - PSA: median 5.7 ng/mL
  - DRE (normal): 96%
  - Diagnosed BPH: 66%
  - Prostate Volume: median 43.4 cc
  - Reason for negative entry biopsy: Rising PSA 95%

Biopsy-Detected Prostate Cancers (ITT)

	Placebo (N=4126)	Dutasteride (N=4105)
Overall	**862 (20.9%)**	**662 (16.1%)**
Overall Hazard Ratio (95% CI)	**0.77 (0.70, 0.85);** p<0.0001	
Relative Reduction in Detection (95% CI)	**22.8% (15.4%, 29.6%)**	

Primary endpoint analysis according to the protocol

Biopsy-Detected Prostate Cancers
in Biopsied Population*

	Placebo (N=3424)	Dutasteride (N=3305)
Overall	858 (25.1%)	659 (19.9%)
Overall Hazard Ratio (95% CI)	0.77 (0.70, 0.85)	
Relative Reduction in Detection (95% CI)	22.8% (15.2%, 29.8%)	

Applicant's sensitivity analysis.

*Including men with at least one on-study biopsy

Clinical Relevance of the Efficacy Results

Issue 1: Increase in High Grade Prostate Cancer

(Assessed with the Original Gleason Scoring System as Published in the NEJM 04/2010)

	Placebo (N=3407)	Dutasteride (N=3299)	p-value*
GS ≤6	617 (18.1%)	437 (13.2%)	<0.0001
GS 7-10	233 (6.8%)	220 (6.7%)	0.81
GS 8-10	19 (0.6%)	29 (0.9%)	0.15

* Nominal p-values, not adjusted for multiple comparisons
Based on the applicant's needle biopsy population

Issue 1: Increase in High Grade Prostate Cancer

(Differences between the Original and Current Gleason Scoring Systems)

Gleason Scoring System	Primary Grade*	Secondary Grade**	Highest Tertiary Grade	Total Score
Original	**3**	**3**	4 or 5	**3+3=6**
Current or Modified (Used in the PCPT)	**3**	3	**4 or 5**	**3+4=7 or 3+5= 8**

* Primary Grade: the most predominant Gleason pattern

** Secondary Grade: the second most predominant Gleason pattern

Issue 1: Increase in High Grade Prostate Cancer

(Requested Reassessment of Tumor Grades with the Current Gleason Scoring)

Key Reasons for Reassessment

- Presence of tertiary grade 4 or 5 in some tumors
- The results based on the original Gleason scoring NOT consistent with today's practice
- Allow comparisons to the results of the finasteride PCPT

Independent Reassessment

- Blinded to both treatment arm and the original Gleason scores
- Review of available needle biopsies for first-time positive prostate cancer diagnosis as determined in the initial read
- Reassessment Rate: 97% of the initial positive biopsies

Issue 1: Increase in High Grade Prostate Cancer

More Evident With the Current Gleason Scoring

(Reassessed Biopsy Population)

	Placebo (N=3388)	Dutasteride (N=3284)	p-value*
Overall	**831 (24.5%)**	**641 (19.5%)**	<0.0001
GS ≤6	**604 (17.8%)**	**434 (13.2%)**	<0.0001
GS 7-10	**227 (6.7%)**	**207 (6.3%)**	0.52
GS 8-10	**16 (0.5%)**	**32 (1.0%)**	0.02

* Nominal p-values, not adjusted for multiple comparisons

The overall consistency rates based on the reread were about 83%

The decrease in GS 7 was observed primarily in GS 3+4: 175 on placebo vs 140 on dutasteride

Issue 1: Increase in High Grade Prostate Cancer

Estimated Treatment to Increased Risk Ratio for High Grade GS 8-10 Tumors:

200:1

If approximately **200** men were treated with dutasteride for 4 years, there would be **1** increase in high grade GS 8-10 prostate cancer

Issue 1: Increase in High Grade Prostate Cancer

Also in the For-Cause Biopsies

	Placebo (N=434)	Dutasteride (N=309)	Difference (%)
GS ≤6	43 (9.9%)	25 (8.1%)	- 1.8%
GS 7-10	27 (6.2%)	28 (9.1%)	+ 2.9%
GS 8-10	2 (0.5%)	8 (2.6%)	+ 2.1%

Exploratory analysis based on the reread Gleason score results.

Issue 2: Risk Reduction Almost Entirely Limited to GS≤6 Tumors

(Pathological Clinical Relevance Evaluation)

- **GS ≤ 6 prostate cancer may represent latent tumors detected on time-mandated, repeated biopsies.**
- **Epstein Criteria** (meeting all the following)
  - GS ≤ 6
  - Absence of GS 4 or 5
  - ≤ 2 positive cores and ≤ 50% involvement of any single core
  - PSA Density < 0.15 ng/mL/cm^3
- **Clinical use of the criteria: to help determine Very Low Risk prostate cancer pathologically:**
  - ➢ Adopted in the NCCN Guidelines-Prostate Cancer

Issue 2: Risk Reduction Almost Entirely Limited to GS≤6 Tumors

Clinical Relevance Evaluation of the GS≤6 Tumors

	Placebo	Dutasteride
GS ≤6 Tumor*	**604**	**434**
Meeting the Epstein's Criteria (Very Low Risk)	**473 (78%)**	**348 (80%)**
Not Meeting or Missing the Criteria (Possibly clinically meaningful)**	**131 (22%)**	**86 (20%)**

*Based on the reread Gleason score results in the reassessment biopsy population of approximately 3300 men each arm. Only GS≤6 tumors diagnosed in both initial read and reread were assessed by Epstein criteria

** Downgraded from GS 7 to GS 6 tumors in the reread

Issue 2: Risk Reduction Almost Entirely Limited to GS≤6 Tumors

Estimated Treatment/Prevention Ratio for Possibly Clinically Relevant Tumors*:

60:1

Approximately **60** men need to be treated with dutasteride for 4 years to reduce **1** possibly clinically meaningful prostate cancer

***based on the decreases in clinically relevant GS≤6 tumor and GS 7 tumor**
For the possibly clinically meaningful GS≤6 tumor reduction only, the ratio= 80:1
For the GS 7 tumor reduction only, the ratio =110:1

Issue 3: Generalizability to Clinical Practice

Scheduled Biopsy (without Cause) at Yrs 2 & 4

- Limited Clinical Value and Problematic:
  - Scheduled biopsy NOT consistent with clinical practice
  - The high prevalence of prostate cancer (40-70%):

    Over-diagnosis of prostate cancer otherwise undetected
  - The results may not be applicable to clinical practice

Issue 3: Generalizability to Clinical Practice

Scheduled Biopsy (without Cause) Results

	Placebo (N=3288)	Dutasteride (N=3202)
GS ≤6	561 (17.1%)	409 (12.8%)
GS 7-10	200 (6.1%)	179 (5.6%)
GS 8-10	14 (0.4%)	24 (0.7%)

Exploratory analysis based on the reread Gleason score results.

Issue 3: Generalizability to Clinical Practice

Applicable to African-American Men?

- Only 2% of the Participants Were Black Men
  - High incidence of prostate cancer in African-American men (232 per 100,000 compared to 146 in White)
  - No risk reduction detected in Black men in the REDUCE trial:
    - Relative risk increased*: 52.1% for Black men

*Subgroup exploratory analysis in Black men

Key Safety Results

- Major safety concern already discussed
  - Increased incidence of high-grade prostate cancers
- Common Adverse Reactions
  - Impotence
  - Decreased libido
  - Breast disorders
  - Ejaculation disorders

Common Treatment-Emergent Adverse Events

(More Frequent on the Dutasteride Arm)

	Placebo (N=4116)	Dutasteride (N=4095)
Impotence	364 (9%)	495 (12%)
Decreased Libido	168 (4%)	282 (7%)
Breast Disorders **Any** **Breast Enlargement** **Breast Tenderness**	 86 (2%) 60 (1%) 35 (<1%)	 159 (4%) 108 (3%) 75 (2%)
Ejaculation Disorders	47 (1%)	144 (4%)

- Reproductive system and breast disorder AEs occurred more frequently on the dutasteride arm
- Overall rates of common AEs, moderate/severe AEs, SAEs, and fatal AEs were similar between arms.

Summary

- Statistically significant reduction in the overall rate of positive biopsy-detectable prostate cancer (~23%; $p<0.0001$) compared to placebo

Benefit/Risk Analysis

- The overall risk reduction almost entirely limited to ≤GS 6 prostate cancers
  - Majority: **very low risk** prostate cancer
  - Estimated Treatment/Prevention Ratio: **60:1**

    (60 men treated in order for 1 man to avoid possibly clinically relevant prostate cancer)

- Evident increases in GS 8-10 prostate cancers
  - In pre-specified, for-cause biopsy, and scheduled biopsy analyses
  - Estimated Treatment/Increased Risk Ratio: **200:1**

    (if 200 men treated, 1 additional incidence of GS 8-10 tumor)

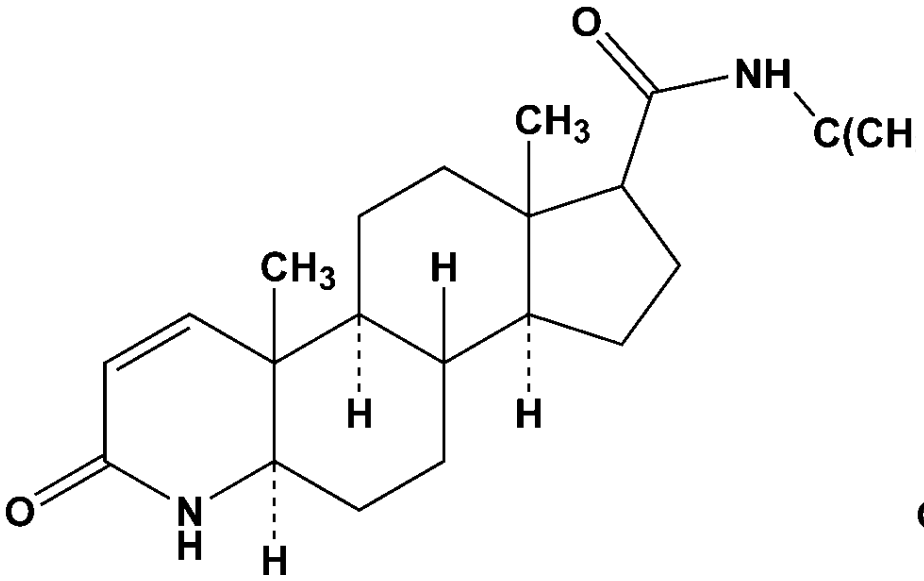
- Generalization of the trial results to clinical practice is questionable.

Comparison of PCPT and REDUCE

ODAC December 1, 2010

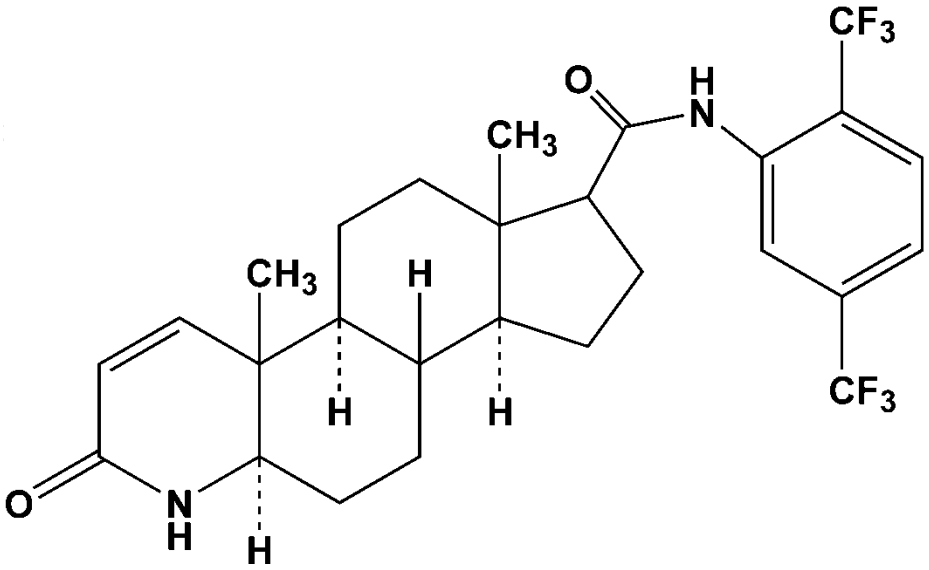
5-α Reductase Inhibitors (5-ARI)

Finasteride



Type II
5-α reductase inhibitor

Dutasteride



Type I & II
5-α reductase inhibitor

Eligibility Criteria

PCPT- "Low to Moderate Risk"

- Men age ≥ 55 y
- Normal DRE
- PSA **≤ 3** ng/mL

- **Allowed:**
  - h/o prostate biopsy(ies)
  - family history 1° relative

- **Excluded:**
  - h/o HG-PIN
  - 5-ARI use

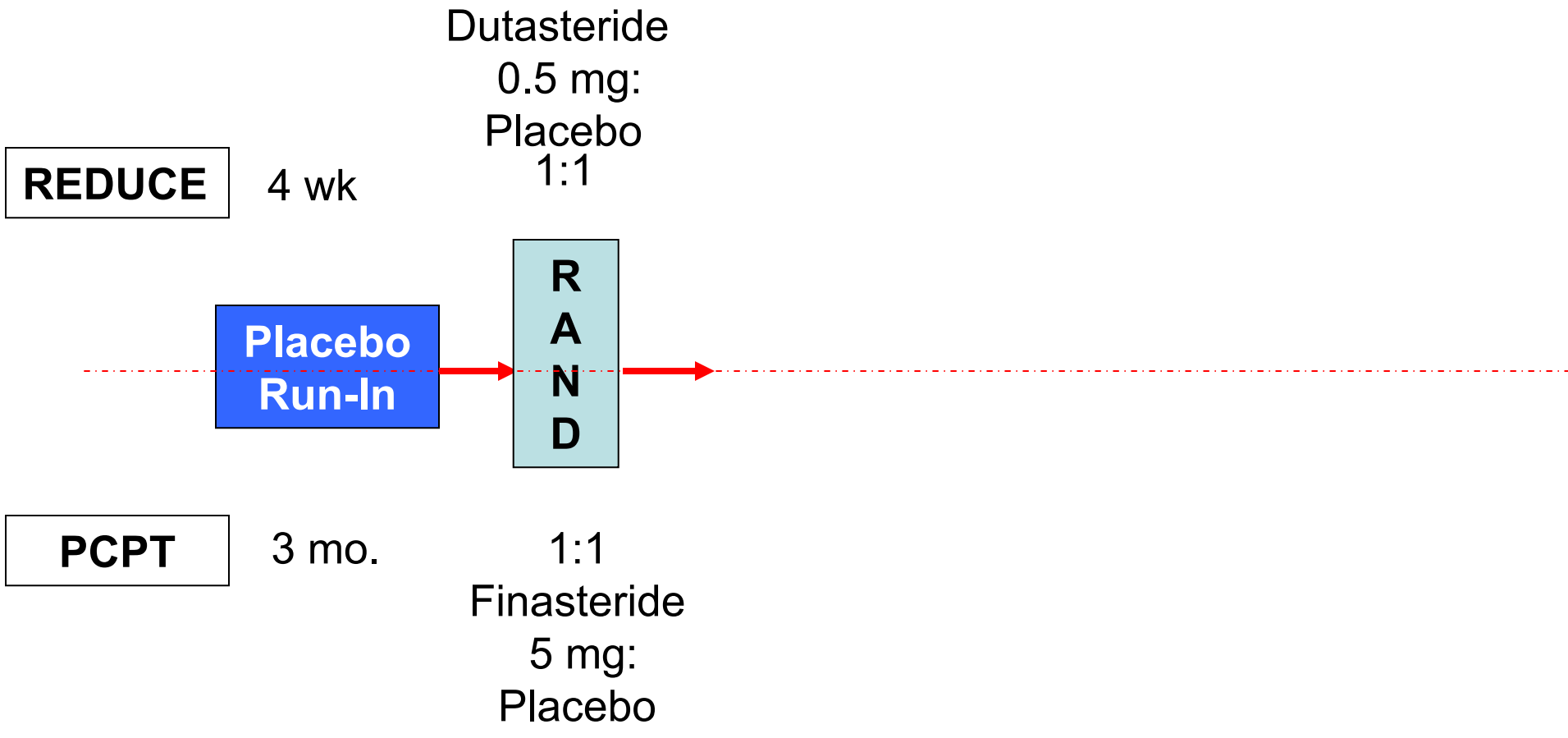
REDUCE- "Increased Risk"

- Men age 50-75 y
- Elevated PSA **(≥ 2.5-10** ng/mL)
- One **single** negative biopsy

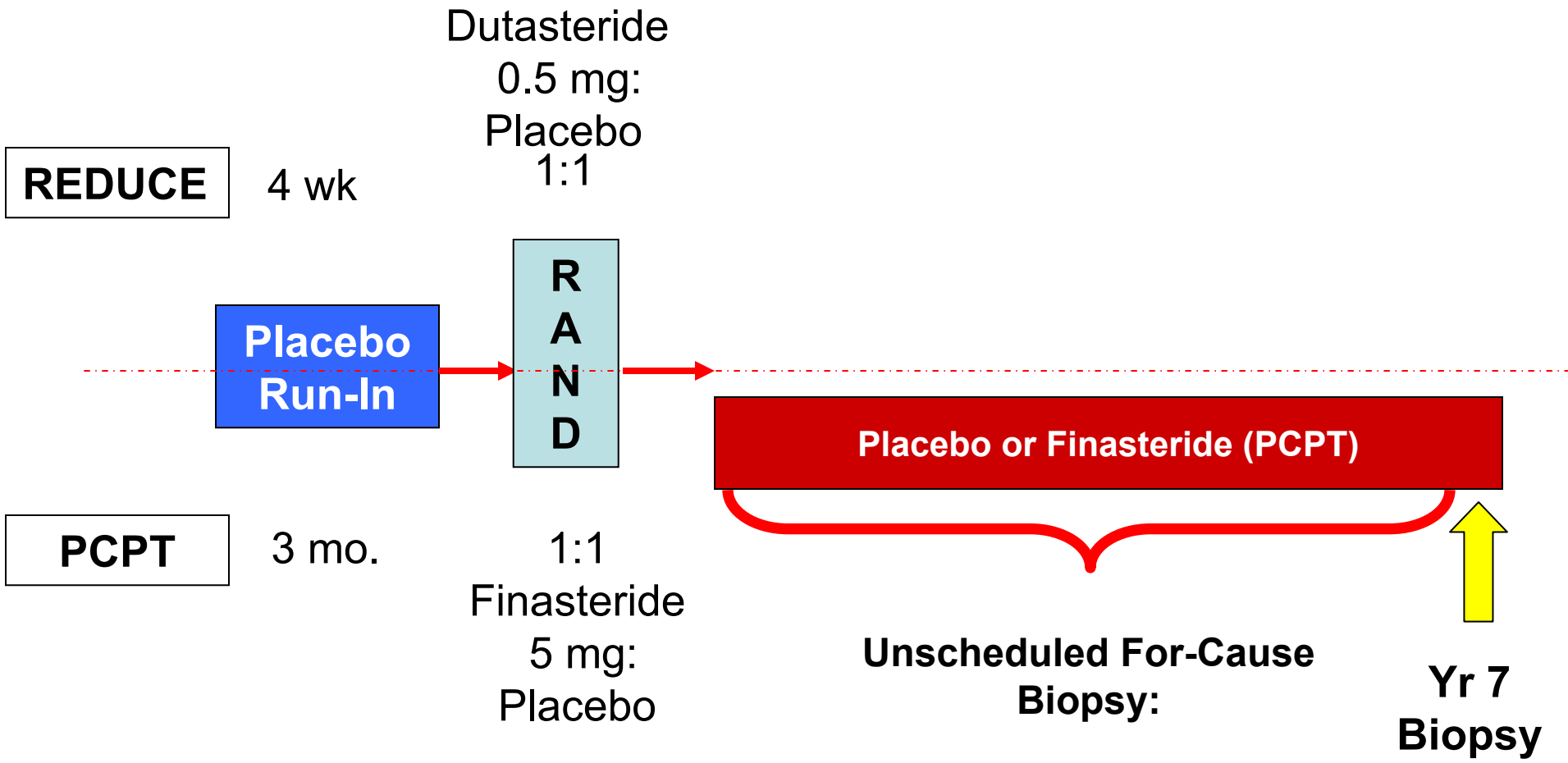
- **Allowed:**
  - abnormal DRE
  - family history 1° relative

- **Excluded:**
  - HG-PIN
  - 5-ARI use

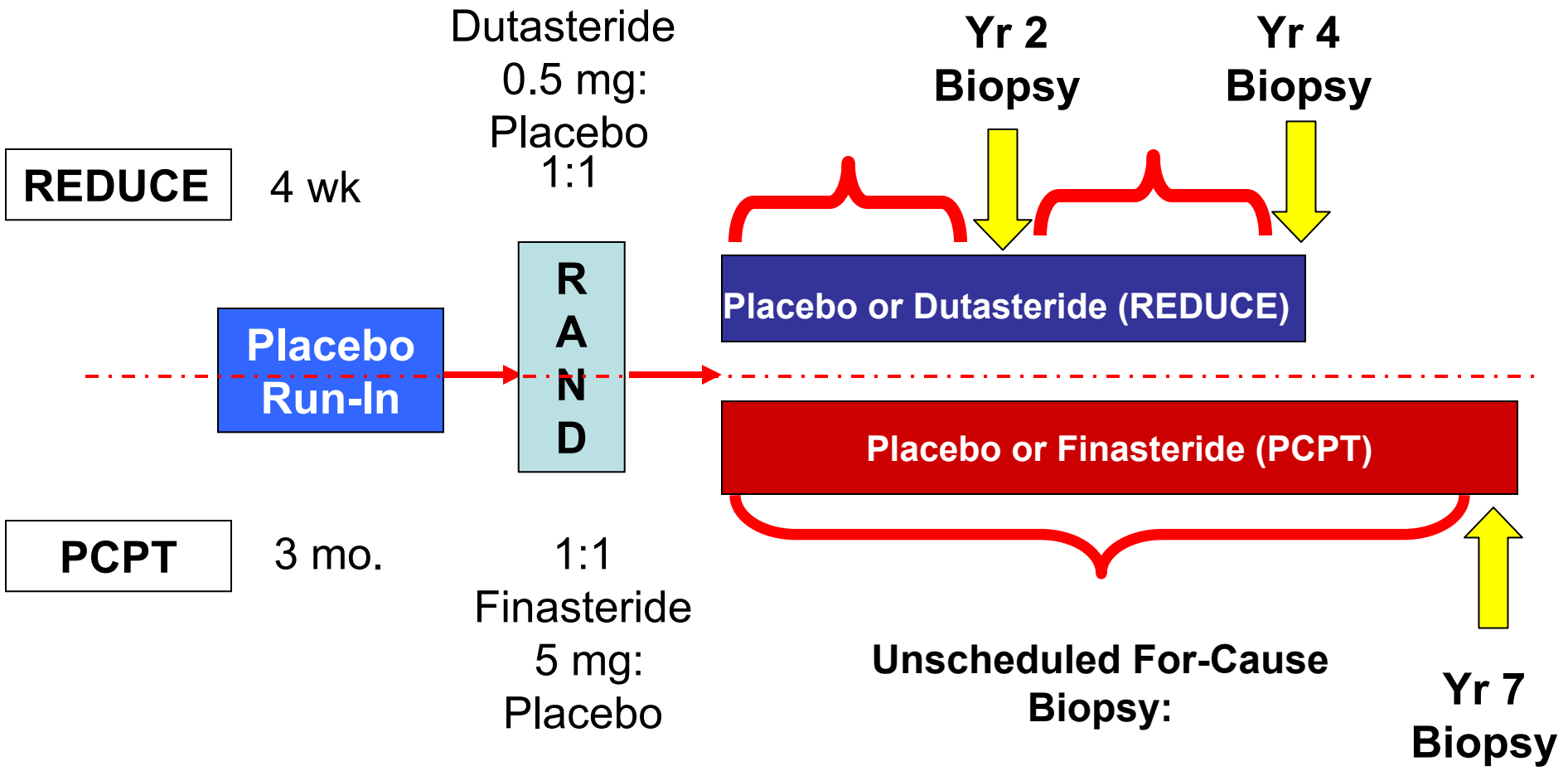
Study Design



Study Design



Study Design



Primary Endpoint, Assessments

- **Primary Endpoint**: Cumulative Incidence of Prostate Cancer

- **Prostate Biopsies**
  - Eligibility: PCPT (allowed) and **REDUCE (one, confirmed neg.)**
  - Scheduled: PCPT (**Year 7**) and **REDUCE (Years 2, 4)**
  - For Cause: PCPT (Elevated PSA or Abnormal DRE) and **REDUCE (investigator discretion)**
  - PSA adjustment on 5-ARI arm: ~Doubled
  - Technique: TRUS guided, **6-core** (PCPT) or **10-core (REDUCE)**

- **Pathology**
  - Central Pathologic Grading:
    - PCPT: **Modified** Gleason Score (GS)
    - REDUCE: **Original Gleason Score**

Baseline Characteristics

	PCPT	REDUCE
Median Age (y)	63	63
Race:		
Caucasian	92%	91%
African American	4%	2%
Other	4%	7%
Prostate Cancer in 1° Relative	15%	10%
Prior Prostate Biopsy	**9%**	**100%**
Median PSA	**1.1 ng/mL**	**5.7 ng/mL**
History of BPH	**26%**	**66%**

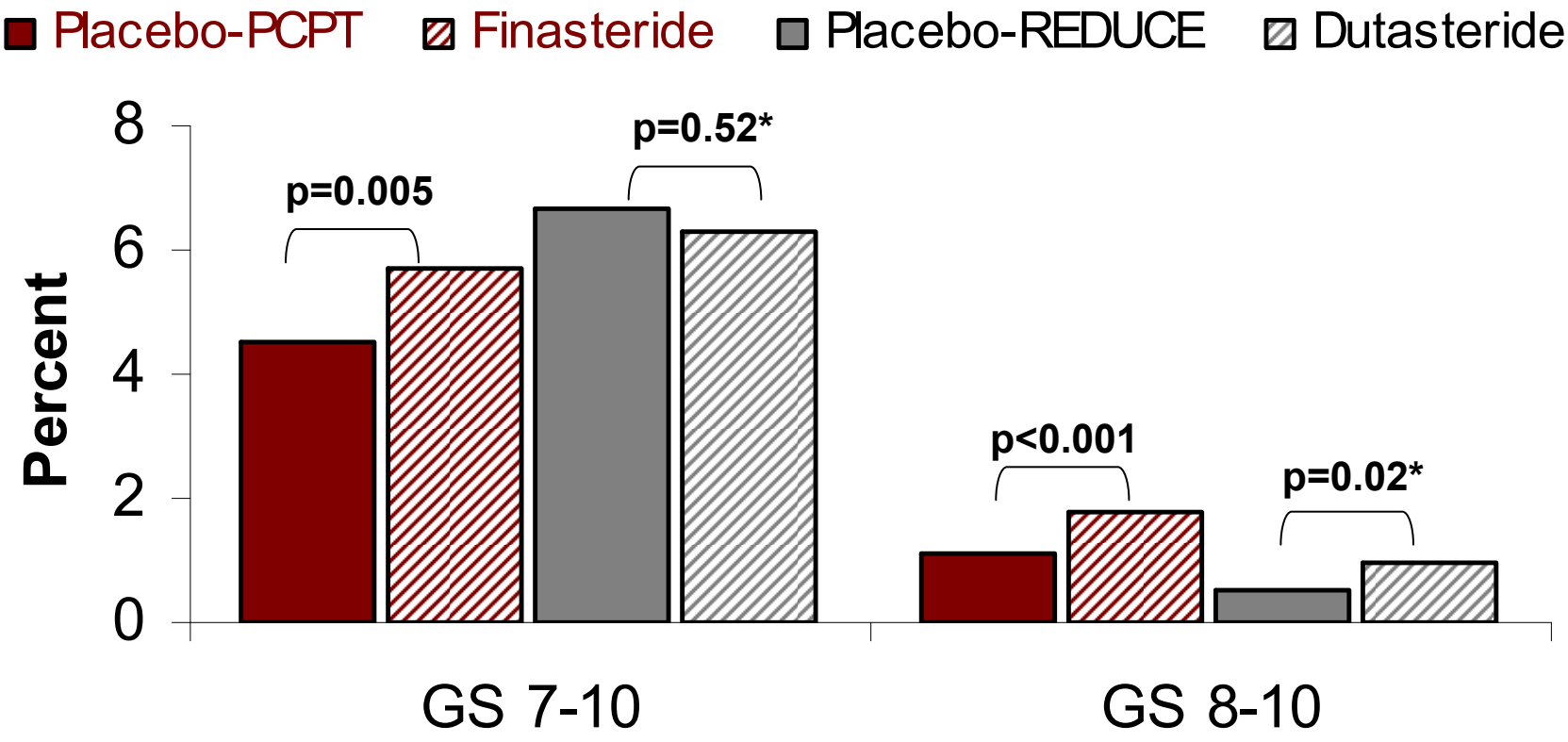
Efficacy Results
All Biopsied Population

- Cumulative Incidence of Prostate Cancer
  - PCPT **16.6% (Finasteride) vs. 22.4% (Pbo)**
  - REDUCE **19.9% (Dutasteride) vs. 25.1% (Pbo)**
- Relative Risk Reduction with 5-ARI
  - PCPT (95% CI) **26% (21%, 32%)**
  - REDUCE (95% CI) **23% (15%, 30%)**

FDA Concerns

- Increase in High-Grade Tumors (GS 8-10)
- Risk Reduction Limited to GS 6 ≤ Tumors
- Generalizability of Results

Increased High-Grade Cancer (GS 8-10)
All Biopsied Population

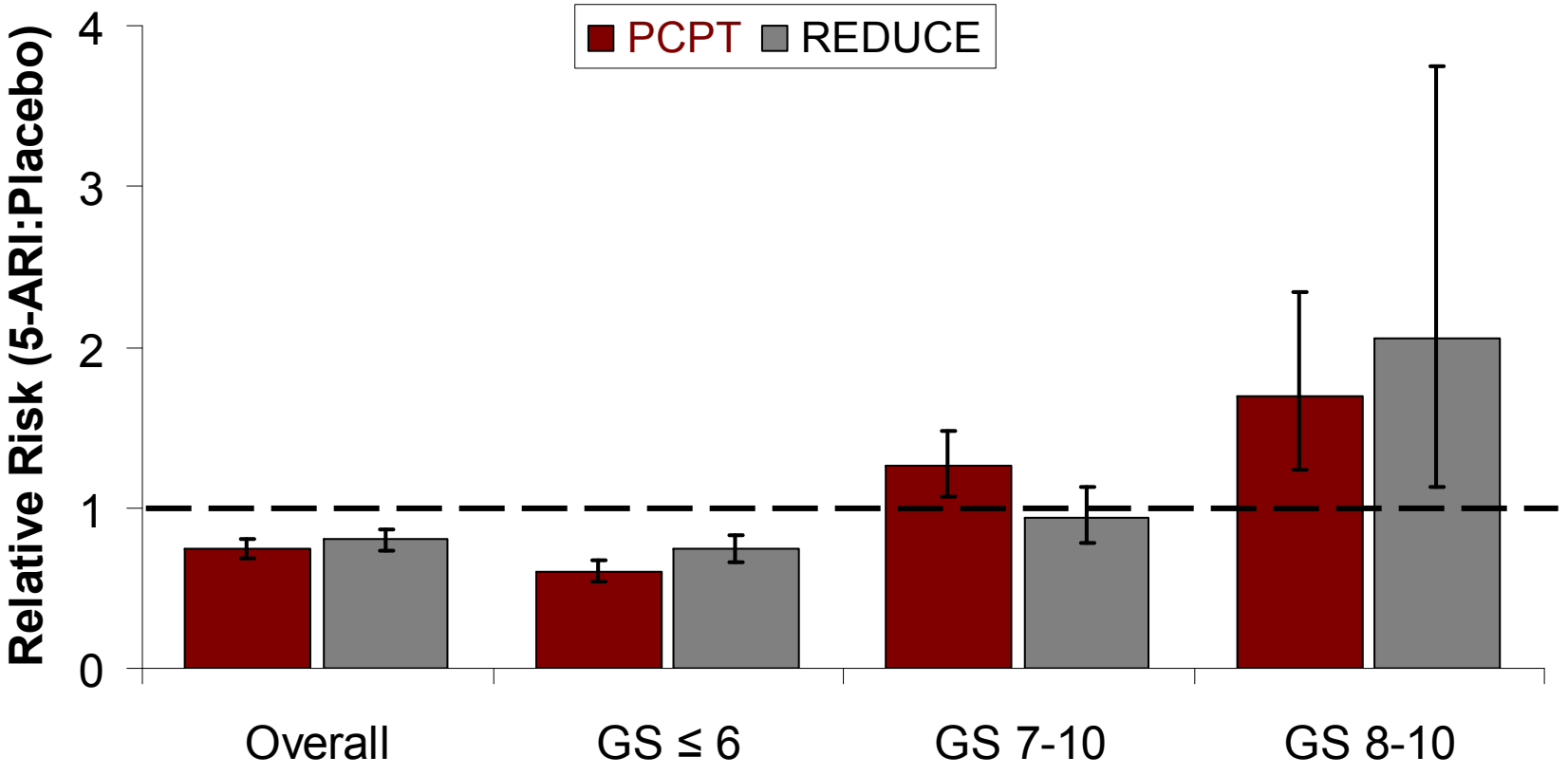


Nominal p-values listed, not adjusted for multiplicity
*Based on re-read results

FDA Concerns

- Increases in High-Grade Tumors (GS 8-10)
- Risk Reduction Limited to GS ≤ 6 Tumors
- Generalizability of Results

Reduction in Risk Limited to GS ≤ 6



Vertical lines represent 95% confidence intervals

FDA Concerns

- Increases in High-Grade Tumors (GS 8-10)
- Risk Reduction Limited to GS ≤ 6 Tumors
- Generalizability of Results

Generalizability of Results

- Most Prostate Cancers Diagnosed on **Scheduled Biopsies**
  - PCPT 56% vs. 40% diagnosed "for cause"
  - REDUCE 91% vs. 9% diagnosed "for cause"

- Increased mGS 8-10 Cancer on **Scheduled Biopsies**

	Placebo	5-ARI
PCPT	11 (0.3%)	25 (0.6%)
REDUCE	14 (0.3%)	24 (0.7%)

Number Needed to Treat (NNT)

PCPT

- Reduction in Risk, Possibly Clinically Meaningful Cancers
  - Defined as All “For Cause” (PSA / DRE)
- Increase in Risk
  - All Gleason score 8-10 cancer

REDUCE

- Reduction in Risk, Possibly Clinically Meaningful Cancers
  - Defined as **NOT** meeting the Epstein pathologic criteria
- Increase in Risk
  - All Gleason score 8-10 cancer

Benefit:Risk

The Number of Men Needed to Treat For:

- Reduction of One Prostate Cancer

  PCPT 39 – 73*

  REDUCE 60

- Development of One GS 8-10 Prostate Cancer

  PCPT 150 – 268*

  REDUCE 200

*NNT range shown for “All Biopsied” and “ITT” populations

Summary

- PCPT and REDUCE Targeted Different Risk Populations
- **Efficacy: ~ 25% Relative Reduction** in Prostate Cancer
  - **Absolute Reduction 5.8%** (PCPT) and **5.2%** (REDUCE)
  - Limited to modified Gleason Score (mGS) ≤ 6 tumors
- **Safety:** Smaller, **Absolute Increase** in HG Tumors
  - PCPT- mGS 7-10 **(1.3%)** or mGS 8-10 **(0.8%)**
  - REDUCE- mGS 8-10 **(0.5%)**
- Risk-Benefit Analysis Considerations

Question to ODAC: Finasteride

Is the finasteride risk/benefit profile favorable for reduction in the risk of prostate cancer in men ≥55 years of age with a normal digital rectal examination and a PSA of ≤3.0 ng/mL?

Question to ODAC: Dutasteride

Is the dutasteride risk/benefit profile favorable for reduction in the risk of prostate cancer in men at increased risk of developing the disease, defined as those who have had a prior negative biopsy due to clinical concern and have an elevated serum prostate-specific antigen (PSA)?